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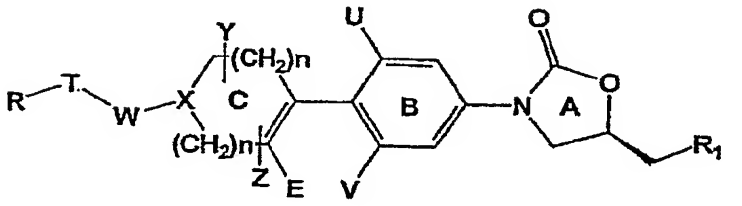
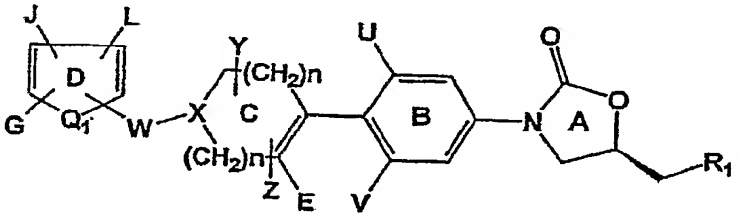
(54) Title: OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS



(I)



(II)

(57) Abstract: The present invention relates to certain substituted phenyl oxazolidinones of formula (I) or (II) and to the processes for the synthesis of the same. This invention also relates to pharmaceutical compositions containing the compounds of the present invention as antimicrobials. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as Bacterioides spp. and Clostridia spp. species, and acid fast organisms such as Mycobacterium tuberculosis, Mycobacterium avium and Mycobacterium spp.

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OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS

FIELD OF THE INVENTION

The present invention relates to certain substituted phenyl oxazolidinones and to the processes for the synthesis of the same. This invention also relates to pharmaceutical compositions containing the compounds of the present invention as antimicrobials. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as Bacterioides spp. and Clostridia spp. species, and acid fast organisms such as Mycobacterium tuberculosis, Mycobacterium avium and Mycobacterium spp.

BACKGROUND OF THE INVENTION

Increasing antibacterial resistance in Gram positive bacteria has presented a formidable treatment problem. The enterococci, although traditionally non virulent pathogens, have been shown, when associated with Vancomycin resistance, to have an attributable mortality of approximately 40%. Staphylococcus aureus, the traditional pathogen of post operative wounds, has been resistant to Penicillin due to production of penicillinases. This resistance was overcome by the development of various penicillinase stable β lactams. But the pathogen responded by synthesizing a modified target penicillin binding protein- 2' leading to less affinity for β lactam antibiotics and a phenotype known as Methicillin Resistant S. aureus (MRSA). These strains, till recently were susceptible to Vancomycin, which inspite of its various drawbacks, has become the drug of choice for MRSA infections. Streptococcus pneumoniae is a major pathogen causing pneumonia, sinusitis and meningitis. Until very recently it was highly susceptible to penicillin. Recently though, different PBP 2' strains with different susceptibility to penicillin have been reported from across the globe.

Oxazolidinones are a new class of synthetic antimicrobial agents which kill gram positive pathogens by inhibiting a very early stage of protein synthesis. Oxazolidinones inhibit the formation of ribosomal initiation complex involving 30S and 50S ribosomes leading to prevention of initiation complex formation. Due to their novel mechanism of

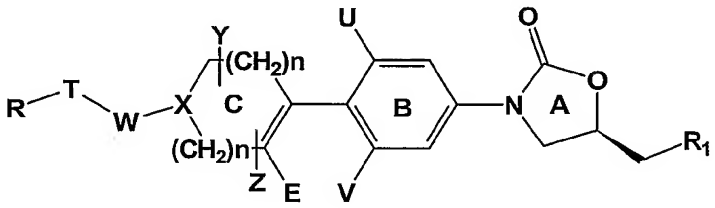
action, these compounds are active against pathogens resistant to other clinically useful antibiotics.

SUMMARY OF THE INVENTION

The invention involves the synthesis; identification and profiling of oxazolidinone molecules which have good activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP. Some of these molecules have activity against MDR-TB and MAI strains, while others have significant activity against important anaerobic bacteria.

The present invention provides processes for the syntheses of phenyloxazolidinone derivatives which can exhibit significant antibacterial activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP against MDR-TB and MAI strains, in order to provide safe and effective treatment of bacterial infections.

In accordance with one aspect of the invention, there are provided compounds having the structure of Formula I



FORMULA I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites,

wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, for example, particular forms of **T** are selected from aryl and five membered heteroaryl which are further substituted by a group represented by **R**, wherein R is H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 is

hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or a C_{0-3} bridging group;

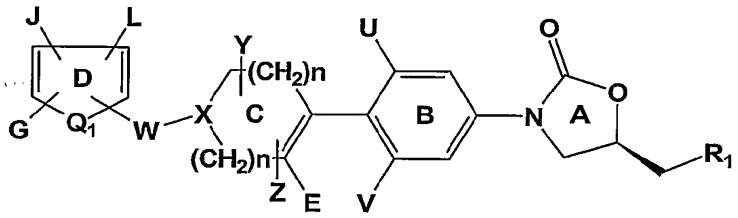
U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is $(CH_2)_{0-n'}$, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2N(R_{11})CH_2-$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(CO)$, NH, O, NR_{11}, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2, SO, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_1 is $-NHC(=O)R_2$, $N(R_3,R_4)$, OR_3, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

Particular compounds of Formula I have R_1 as acetamide, halogen, ether linked heteroaryl or amino-heteroaryl, substituted acetamide and the most preferred compounds in this series would be prepared as the optically pure enantiomers having the (S)-configuration according to the Cahn-Ingold-Prelog notation at C_5 of the oxazolidinone ring.

Other particular compounds of Formula I containing D ring as furanyl, thienyl, and pyrrolyl ring systems and further substituted by substitutions G, J and L are represented by Formula II



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R_1** can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3; and R_3, R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

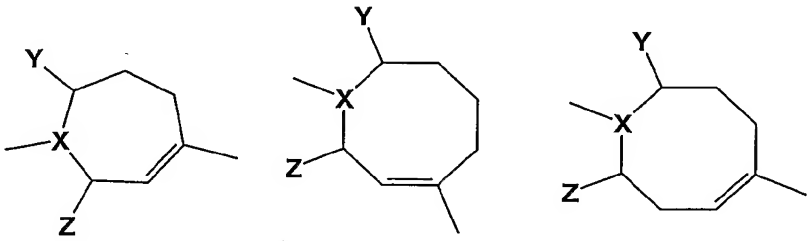
W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

Q_1 is O, S or NR_{11}, wherein R_{11} is as defined above;

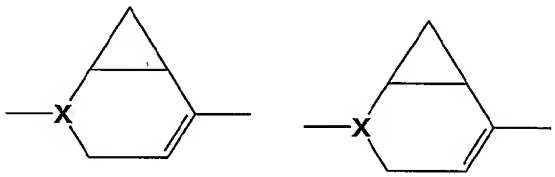
G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4, SR_4, wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

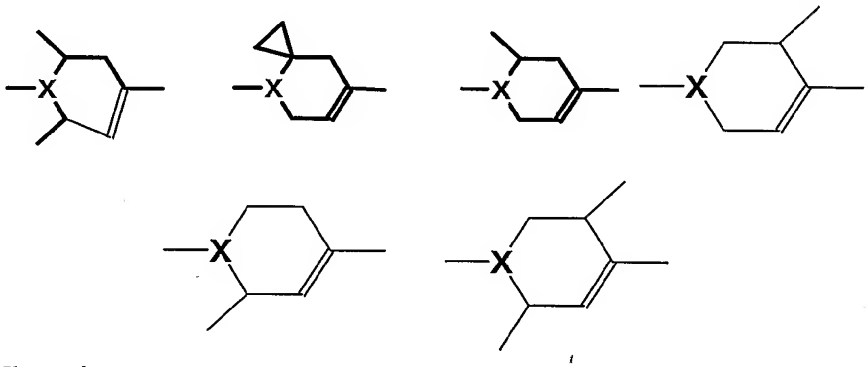
In some compounds represented by Formula II, ring C may be 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, for example:



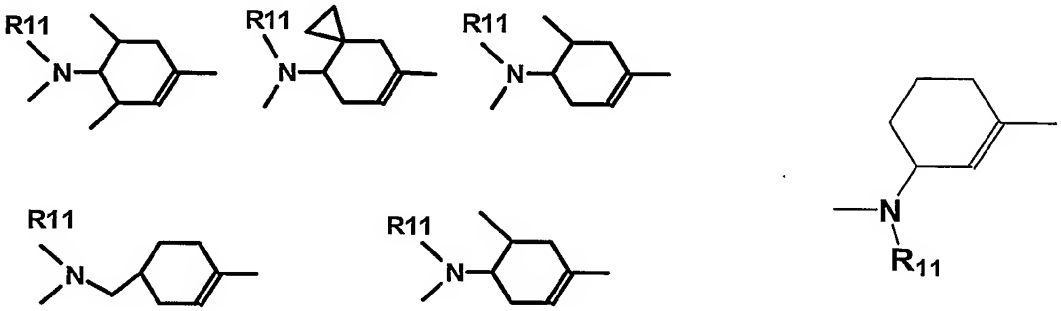
The ring C may be bridged to form a bicyclic system as shown below:



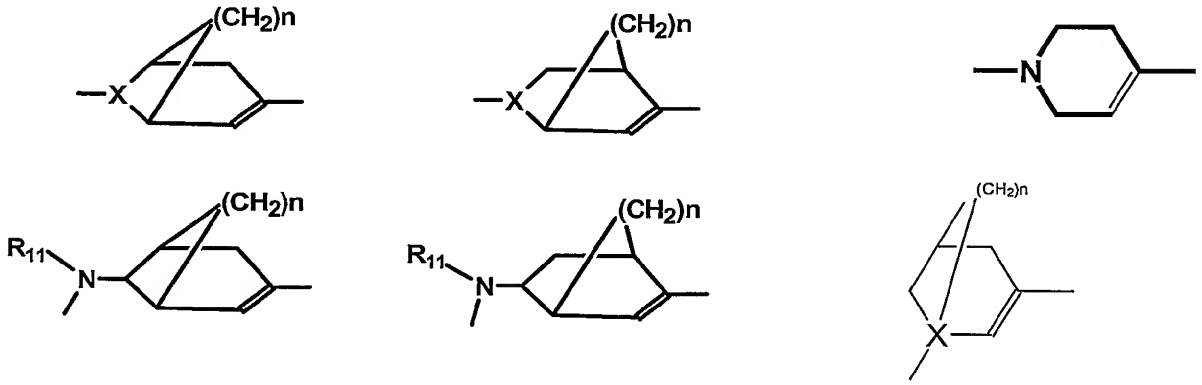
When ring C is optionally substituted at positions Y and Z, particular examples with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups are as shown below:



When ring C is 6-membered in size and X is -CH-(NHR), or -$CHCH_2NHR$-, the following rings are preferred ones wherein R_{11} is as defined earlier.

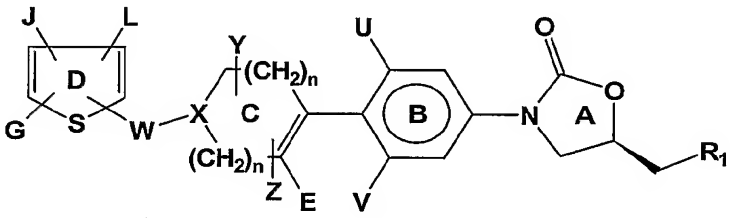


In addition to the above, ring C also includes the following structures:



Wherein n is as defined earlier.

In accordance with a third aspect of the present invention, there are provided compounds represented by Formula III



Formula III

wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3,R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$ wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R_1** can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3; and R_3, R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, or a C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$; wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 is the same as above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

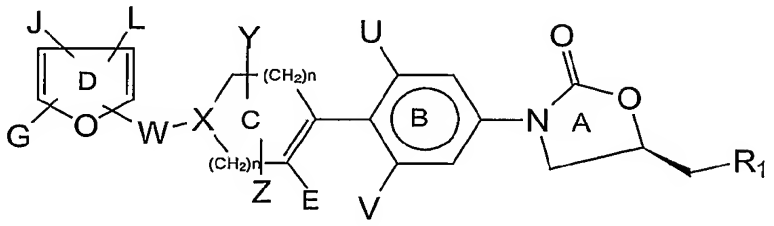
Particular G, J and L substitutions can include nitro, aldehydes and halides.

Other particular compounds of Formula III are as follows:

Compound No 2: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl (5-nitro) methyl)} 1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Compound No 3: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide.

In accordance with a fourth aspect of the present invention, there are provided compounds represented by Formula IV



Formula IV

wherein

R_1 is –NHC(=O)R_2, -N(R_3, R_4), –$NR_2C(=S)R_3$, –$NR_2C(=S)SR_3$, –OR_3 wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R_1** can be of the formula –NH(C=O)R_2 wherein R_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3; and R_3, R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

Q_1 is O, S or NR_{11}, wherein R_{11} is as defined earlier;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6,R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 is as above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_1=$_6$ alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

Particular G, J and L substitutions are nitro, aldehydes and halides.

A particular compound of Formula IV is

Compound No. 5: 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one.

Compounds of the present invention can be useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic Gram-positive bacteria, including multiply-antibiotic resistant staphylococci and streptococci as well as anaerobic organisms such as Mycobacterium tuberculosis and other mycobacterium species.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, suppositories and ointments. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders or tablets disintegrating agents; it can also be as finely divided solid which is in admixture with the finely divided active compound. For the preparation of tablets, the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets

preferably contain from about 5 to about 70 percent of the active ingredient. Suitable solid carriers are lactose, pectin, dextrin, starch, gelatin, tragacanth, low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Such solutions are prepared so as to be acceptable to biological systems (isotonicity, pH, etc.). Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents as desired. Aqueous suspension suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e. natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose and other well-known suspending agents.

Ointment preparations contain heavy metal salts of a compound of Formula I with a physiologically acceptable carrier. The carrier is desirably a conventional water-dispersible hydrophilic or oil-in-water carrier, particularly a conventional semi-soft or cream-like water-dispersible or water soluble, oil-in-water emulsion infected surface with a minimum of discomfort. Suitable compositions may be prepared by merely incorporating or homogeneously admixing finely divided compounds with the hydrophilic carrier or base or ointment.

The pharmaceutical preparations can be in unit dosage form. In such forms, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete capsules, powders in vials or ampoules, and ointments capsule, cachet, tablet, gel, or cream itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from less than 1 mg to several grams according to the particular application and the potency of the active ingredient.

In therapeutic use as agents for treating bacterial infections, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 3 mg to about 40 mg per kilogram daily. The dosages, however, may be varied depending upon the requirements of the patient and the compound being employed. Determination of the proper dosage for a particular situation is within the smaller dosages which are less than the optimum dose. Small increments until the optimum effect under the daily dosage may be divided and administered in portions during the day if desired.

In one aspect, the invention provides process for the syntheses of compounds of Formulae I, II, III and IV. Pharmaceutically acceptable non-toxic acid addition salts of the compounds of the present invention of Formulae I, II, III and IV may be formed with inorganic or organic acids, by methods well known in the art.

The present invention also includes within its scope prodrugs of the compounds of Formulae I, II, III and IV. In general, such prodrugs will be functional derivatives of these compounds which readily get converted *in vivo* into defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan of ordinary skill in the art.

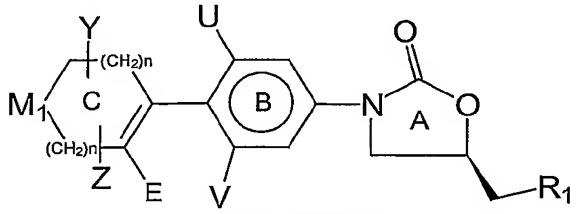
The invention also includes pharmaceutically acceptable salts, the enantiomers, diastereomers, N-oxides, metabolites in combination with pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description, or may be learned by the practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

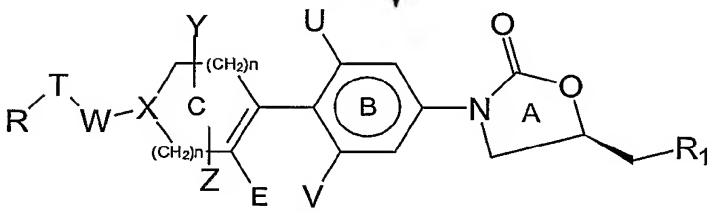
The compounds of the present invention may be prepared by following the reaction sequences as depicted in the schemes defined below.

SCHEME-I



Formula V

$R—T—W—R_{12}$



FORMULA-I

In scheme I, the amine of Formula V wherein M_1 is NH, NHR_{13}, $-CH_2NHR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy;

R_1 is $–NHC(=O)R_2$, $-N(R_3, R_4)$, $–NR_2C(=S)R_3$, $–NR_2C(=S)SR_3$ or $–OR_3$, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R_1** can be of the formula $–NH(C=O)R_2$ wherein R_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3; and R_3, R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl,or pyridyl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I,

is reacted with a heteroaromatic compound of Formula R-T-W-R_{12} wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, for example, particular forms of **T** are selected from aryl and five membered heteroaryl which are further substituted by a group represented by **R**, wherein R is H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more F, Cl, Br, I, OR_4, SR_4, wherein R_4 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_{12} is a suitable leaving group well known to one of ordinary skill in the art such as fluoro, chloro, bromo, SCH_3, -SO_2CH_3, -SO_2CF_3, Tos, OC_6H_5, –COOH or –CHO-.

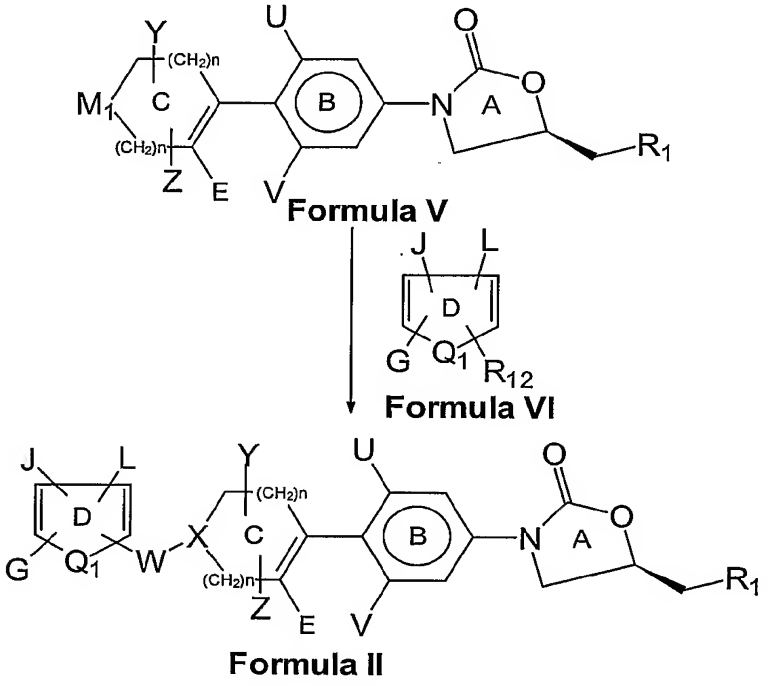
For the preparation of compounds of Formula I when W is equal to CH_2, the corresponding aldehyde can be used through a process of reductive amination and is attached to the amine of Formula V.

Similarly, for the preparation of compound of Formula I wherein W is equal to C = O, the corresponding acid can be used and the amine of Formula V can be acylated

through activated esters in the presence of condensing agents, for example, 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). Other methods of acylation can also be employed.

The preparation of the compound of Formula II can be accomplished as exemplified below by two methods A and B as shown in Scheme II:

SCHEME-II



Method A:

The amine of Formula V wherein M_1 is NH, NHR_{13}, $-CH_2NHR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy;

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R_1** can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3; and R_3, R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I,

is reacted with a heteroaromatic compound of Formula VI wherein

R_{12} is a suitable leaving group such as fluoro, chloro, bromo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$, Tos, OC_6H_5, –COOH or –CHO-, other suitable leaving groups are well known to one of ordinary skill in the art;

$\mathbf{Q_1}$ is O, S or NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, $-CH = N-OR_{10}$, $-C=CH-R_5$, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4, SR_4, wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

The reaction can be carried out in a suitable solvent, for example, dimethylformamide, dimethylacetamide, ethanol or ethylene glycol at a suitable temperature in the range of about -70°C to about 180°C to afford compounds of Formula II. The presence of a suitable base such as triethylamine, diisopropylamine, potassium carbonate, sodium bicarbonate is useful in some cases to improve the yield of the reaction.

The reductive alkylation of the amine intermediate of Formula V with the corresponding heterocyclic aldehydes of the Formula VI, such as furaldehyde (Q_1 = O, R_{12} is CHO) using reducing agents well known to one of ordinary skill in the art such as sodium triacetoxyborohydride or sodium cyanoborohydride gives the products of Formula II, wherein W=CH_2 as shown in the Scheme II.

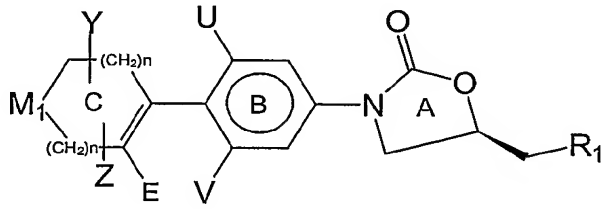
Method B:

The acylation of intermediate amines of Formula V with a heterocyclic acid of Formula VI, such as 2- furoic acid (Q_1 = O; Q_2 = C; G, J, L = H; R_{12} =COOH) gives products of Formula II, wherein W=CO, as shown in the Scheme II wherein U, V, Y, Z, X, W, Q1, G, J, L, R_{12} and E are as defined earlier.

Alternatively, the compounds having carbonyl link can also be made by reacting heteroaromatic compound of the Formula VI, such as N-methyl pyrrole with the intermediate amine of Formula V, in the presence of triphosgene or phosgene. The carbonyl linkers may also be introduced between heteroaromatic compound, such as 3-bromothiophene and the amine of Formula V with carbon monoxide in the presence of a catalyst, such as Pd $(PPh_3)_2Cl_2$. The extended chain pyrroles having dicarbonyl linkers can also be obtained from treatment with oxalyl chloride and the amine of the Formula V.

The reduction of the carbonyl linkers using the standard reducing agents results in the formation of methylene linkers.

Mainly amine of Formula V



Formula V

was used for the preparation of compounds of Formula I and Formula II, for example following two specific amines, identified as two different cores, namely

(S)-N-[[3-[3-Fluoro-4-[N-1-(1,2,5,6-tetrahydropyrid-4-yl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (**Core I**)

5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one (**Core II**)

were used for the preparation of analogs.

The key intermediate amines of Formula V for the analogue preparation were prepared from commercially available reagents, wherein M_1 is NH, NHR_{13}, $-CH_2NHR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R_1, U, V, Y, Z and E are as defined earlier.

Some amines of Formula V are already known in the literature and are given by reference and if they have been made for the first time or by different procedures or variation of known procedure, they are described in detail in the experimental section.

The optically pure amines of Formula V could be obtained either by one of a number of assymetric syntheses or alternatively by resolution from a racemic mixture by selective crystallization of a salt prepared, with an appropriate optically active acid, such as dibenzoyl tartrate or 10-camphorsulfonic acid, followed by treatment with base to afford the optically pure amine.

The transformations effected are described in the experimental section. In the above synthetic methods, where specific acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. are mentioned, it is to be understood that the other acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. may be used. Similarly, the reaction temperature and duration of the reaction may be adjusted according to the desired need.

Particular compounds which are capable of being produced by the above mentioned schemes include:

Compound No. **Chemical Name**

1. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl}1,2,5,6-tetrahydropyrid-4-yl] phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

2. (S)-N-[[3-[3-Fluoro- 4-[N-1-{2-thienyl (5-nitro) methyl)}1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

3. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide,

4. 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl] 1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one,

5. 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one.

Most of the compounds were characterized using NMR, IR and were purified by chromatography. Crude products were subjected to column chromatographic purification using silica gel (100-200 or 60-120 mesh) as stationary phase.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation for the particular compounds. The examples are given to illustrate the details of the invention and should not be constrained to limit the scope of the present invention as defined by the claims.

EXAMPLE 1

Analogs of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Core I)

(S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide (core I) was prepared according to procedures described in PCT patent application WO 97/30995 and U.S. Patent No. 6,051,716.

Method A:

General Procedure:

The reductive alkylation of the amine intermediate of Formula V with the corresponding heterocyclic aldehydes of the Formula VI, using known reducing agents well known to one of ordinary skill in the art such as sodium triacetoxyborohydride or sodium cyanoborohydride gave the products of Formula II wherein W=CH_2.

The following compounds were made using this method:

Compound No.1: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl}1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

To a solution of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride (0.14 g, 0.38 mmol) in tetrahydrofuran (10 mL), 5-nitro-2-furaldehyde (0.081g, 0.57 mmol) and molecular sieves added and stirred at RT for 30 min. Then, sodium triacetoxyborohydride (0.32 g, 1.53 mmol) was added and further stirred for 17hrs. The reaction mixture was filtered and the filtrate evaporated in vacuo. The residue obtained was dissolved in dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was purified by column chromatography, eluting with 2% MeOH/dichloromethane.

^{1}H NMR($CDCl_3$) δppm: 7.4 (d, 1H, Ar-H), 7.1-7.3 (3H, Ar-H), 6.4 (d, 1H, Ar-H), 6.1 (t, 1H, NH), 6.0 (s, 1H, double bond H), 4.7 (m, 1H, CH), 4.1 (t, H, CH), 3.4-3.8 (m, 5H), 3.4 (m, 2H, CH_2), 2.8 (m, 2H, 4.1 (t, H, CH), 3.4-3.8 (m, 5H), 3.4 (m, 2H, CH_2), 2.8 (m, 2H, CH_2), 2.6 (m, 2H, CH_2), 2.0 (s, 3H, CH_3).

Compound No 2: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl(5-nitro)methyl)}1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The title compound was prepared using (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and 5-nitro-2-thiophenecarboxaldehyde according to Method A, Compound No. 1.

H^1 NMR ($CDCl_3$) δppm: 6.0-7.8 (m, 5H, Ar-H) 6.0 (m, 2H (NH and double bond H) 4.79 (m, 1H, CH), 4.18 (t, 2H, CH_2) 3.6-3.8 (m, 5H), 3.2 (m, 2H, CH_2) 2.7 (m, 2H, CH_2), 2.4 (m, 2H CH_2), 2.0 (s, 3H, CH_3).

Method B

General Procedure:

For the preparation of compound of Formula I wherein W is equal to C = O, the corresponding acid of Formula VI is used and the amine of Formula V is acylated through

activated esters in the presence of condensing agents such as 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), along with 1-hydroxybenzotriazole. Other methods of acylation can also be employed.

The following compounds were prepared using this method:

Compound No 3: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydro pyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide.

To a solution of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride (0.18 g, 0.49 mmol) in N,N-dimethyl formamide which was cooled to 0°C, N-methylmorpholine (0.16g, 1.57 mmol), and 1-hydroxybenzotriazole (0.065g, 0.49 mmol) were added and stirred for 30 min. Then, 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was added and the reaction mixture was stirred at room temperature for 17hrs. The reaction mixture was evaporated in vacuo and the residue was taken in dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude product was purified by column chromatography, eluting with 2% MeOH/dichloromethane.

^{1}HNMR($CDCl_3$) δppm: 7.8 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H) 7.2 (m, 3H, Ar-H), 6.0 (t, 1H, NH), 6.0 (broad, s, 1H, double bond H), 4.7 (m, 1H, CH), 3.7-4.5 (m, 8H, CH2), 2.6 (m, 2H, CH2) 2.6 (m, 2H, CH2), 2.0 (s, 3H, CH_3)

IR: 1704, 1605 cm^{-1}

EXAMPLE 2

Analogs of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one (Core II)

The amine, 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one was prepared according to the procedure described in PCT patent application WO 00/21960.

Compound No.4: 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl] oxazolidin-2-one

To a solution of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one hydrochloride (0.43 gm, 0.905 mmole) in tetrahydrofuran (10 ml), was added 5-nitro–furan–2-carboxaldehyde (0.191gm, 1.35 mmole) and molecular seive (0.4 gm) at room temperature. The reaction mixture was stirred for half an hour. It was followed by the addition of sodium triacetoxy borohydride (0.575 gm, 2.715 mmole) and further stirred for 3hrs. The reaction mixture was filtered, washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated solution of sodium bicarbonate, followed by washing with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product obtained was purified by column chromatography, eluting with 1% methanol in dichloromethane.

Yield = 0.4gm.

^{1}HNMR ($CDCl_3$) δppm: 8.25 (d, 1H), 7.38 (d, 1H), 7.21-7.15 (m, 2H), 6.54 (d, 2H), 5.95 (m, 1H), 6.07 (m, 1H), 4.71 (d, 1H), 4.35-4.33 (t, 1H), 4.14-4.06 (m, 2H), 3.82-3.78 (m, 2H), 3.27-3.26 (m, 2H), 2.82-2.78 (m, 2H), 2.57 (m, 2H), 1.55 (s, 9H)

Compound No. 5: 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl) methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one

To a solution of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one (0.4 g, 0.69 mmol) in dichloromethane at 0 °C, trifluoroacetic acid was added and the reaction mixture was stirred at room temperature for 3 hrs. The reaction mixture was evaporated in vacuo. The residue was taken in ethyl acetate and neutralized with ammonium hydroxide, and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo. The crude product was purified by column chromatography, eluting with 1% MeOH in dichloromethane to yield 0.16 g of the title product.

^{1}H NMR ($CDCl_3$) δppm: 8.06 (d, 1H), 7.41-7.16 (m, 4H), 6.54 (d,1H), 5.95 (m,1H), 5.87 (m,1H), 4.95 (m, 1H), 4.72 (d, 1H), 4.39 (m, 1H), 4.08 (t,1H), 3.87-3.71 (m, 3H), 3.63-3.61 (m, 1H), 3.27-3.26 (m, 2H), 2.82-2.78 (m, 2H), 2.56 (m, 2H).

EXAMPLE 3

Pharmacological Testing

The compounds of the invention display antibacterial activity when tested by the agar incorporation method. The following minimum inhibitory concentrations (μg/ml) were obtained for representative compounds of the invention which are given below in the following Table 1.

GUIDE TO TABLE ABBREVIATIONS:

1) *S.aureus* ATCC 25923 --*Staphylococus aureus* ATCC 25923

2) MRSA 15187 --Methicillin Resistant *Staphylococcus aureus*

3) *Ent. faecalis* ATCC 29212 --*Enterococcus faecalis* ATCC 29212

4) *Ent. faecium* 6A -- *Enterococcus faecium 6A Van®,Cipro®*

5) *Strep. pne.* ATCC 6303 --*Streptococcus pneumoniae* ATCC 6303

6) *Strep.pyog.* ATCC 19615 --*Streptococcus pyogenes*

7) S. epidermidis - *Staphylococcus epidermidis* ATCC 12228

TABLE - 1

In vitro minimum inhibitory concentrations (µg/ml)

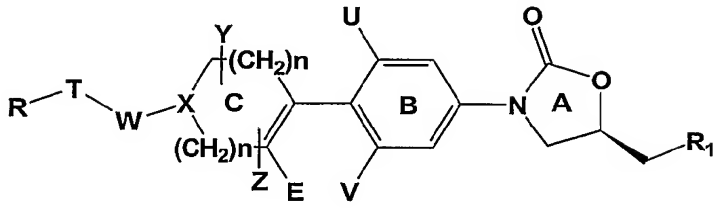
Compound No.	S.aureus 25923	MRSA 15187	MRSA 562	MRSA 33	E. faecalis	VRE	S.pyogenes 19615	S.pneum 6303	S.pneum AB 34
1.	1	0.5	0.5	1	1	1	<0.125	0.5	0.5
3.	<0.125	<0.125	<0.125	<0.125	0.25	0.25	<0.125	0.25	0.5
2.	2	2	1	1	2	2	0.125	0.5	1
5.	1	1	1	1	1	1	1	1	1
Linezolid	2	1	2	2	2	2	2	2	4
Vancomycin	1	0.5	0.5	0.5	4	>16	0.5	0.5	0.25

The in vitro antibacterial activities of the compounds were demonstrated by the agar incorporation method (NCCLS M 7 and M 100-S8 documents). Briefly, the compounds were dissolved in dimethylsulfoxide and doubling dilution of the compounds were incorporated into Meer Hilton agar before solidification. Inoculum was prepared by suspending 4 to 5 colonies into 5 ml of normal saline solution and adjusting the turbidity to 0.5 Macfarland turbidity standard tables (1.5×10^8 CFU/ml), after appropriate dilutions, 10^4 CFU/spot was transfered into the surface of dried plate and incubated for 18 hours (24 hours for MRSN studies). The concentration showing no growth of the inoculated culture was recorded as the MIC. Appropriate ATCC standard strains were simultaneously tested and the result recorded only when the MIC's against standard antibiotics were within the acceptable range.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. Compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, polymorphs, enantiomers, diastereomers, N-oxides, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and further substituted by a group represented by **R**, wherein R is H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more F, Cl, Br, I, OR_4, SR_4, wherein R_4 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

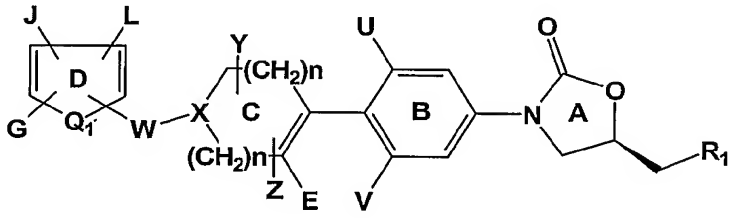
Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is $(CH_2)_{0-n'}$, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, S, $CH_2(CO)$, NH, O, NR_{11}, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2, SO, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_1 is $-NHC(=O)R_2$, $N(R_3,R_4)$, OR_3, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

2. Compounds having the structure of Formula II:



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3,R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy,

aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$,wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

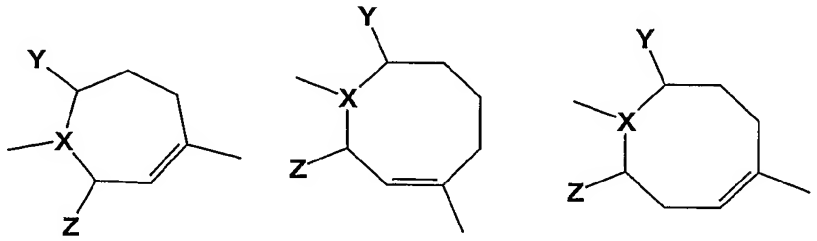
W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

$\mathbf{Q_1}$ is O, S or NR_{11}, wherein R_{11} is as defined above;

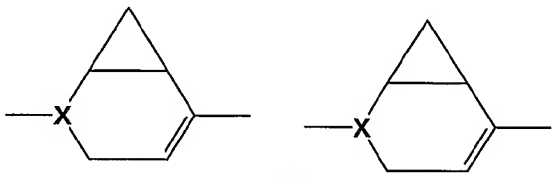
G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4, SR_4, wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

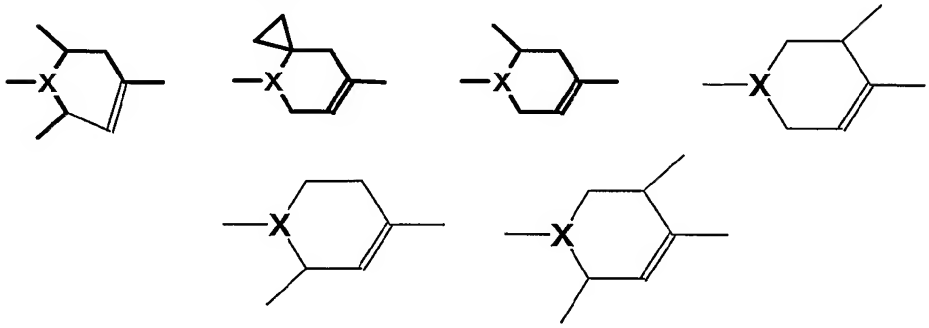
3. A compound according to claim 2, wherein in Formula II, ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, comprising:



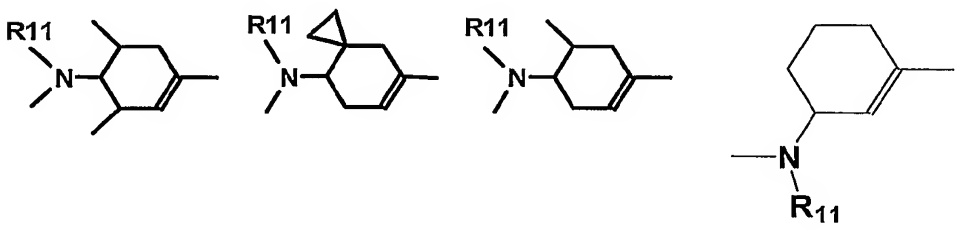
and the ring C may be bridged to form a bicyclic system as shown below:



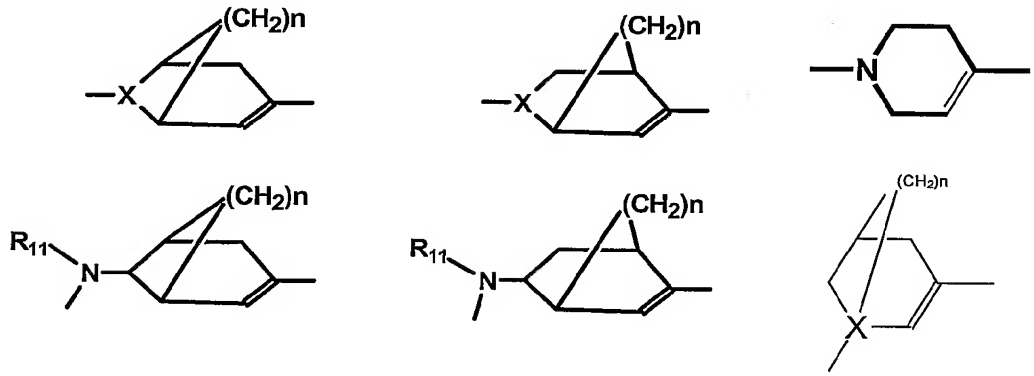
4. A compound according to claim 2, wherein in Formula II, ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below:



5. A compound according to claim 2, wherein in Formula II, ring C is 6-membered in size and X is -CH-(NHR), or -$CHCH_2NHR$-, the ring C is selected form the group consisting of the following rings wherein R_{11} is as defined earlier,

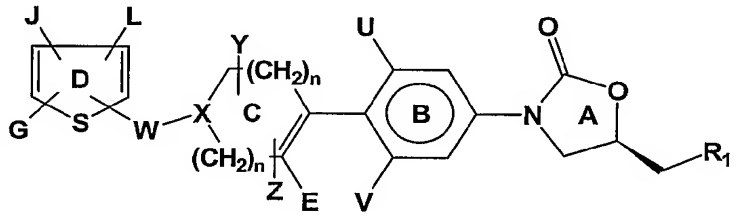


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

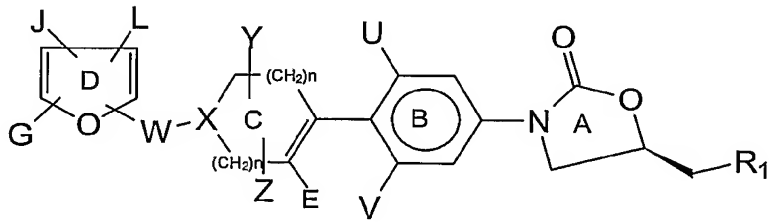
6. A compound according to claim 2 having the structure of Formula III,



Formula III ,

wherein R, U, V, Y, Z, E, X, W, G, J, L and n are as defined earlier.

7. A compound according to claim 2 having the structure of Formula IV,



Formula IV

wherein R_1, U, V, X, Y, Z, E, W, G, J, L and n are as defined earlier.

8. A compound selected from the group consisting of:

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl}1,2,5,6-tetrahydropyrid-4-yl] phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound No. 1)

(S)-N-[[3-[3-Fluoro- 4-[N-1-{2-thienyl (5-nitro) methyl)}1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound No. 2)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (Compound No. 3)

5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one (Compound No. 4)

5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one (Compound No. 5).

9. A pharmaceutical composition comprising a compound of claims 1, 2, or 8 and a pharmaceutical acceptable carrier.

10. A pharmaceutical compositon comprising a pharmaceutically effective amount of a compound according to claims 1, 2 or 8 or a physiologically acceptable acid addition salt thereof with a pharmaceutically acceptable carrier for treating microbial infections.

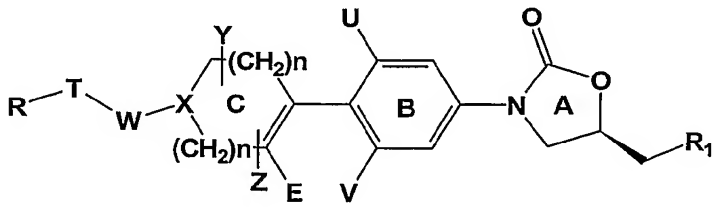
11. A method of treating or preventing microbial infections in a mammal comprising administering to said mammal, the pharmaceutical composition according to claim 9.

12. The method according to claim 11, wherein the microbial infections are caused by gram-positive and gram-negative bacteria.

13. The method according to claim 12, wherein the gram-positive bacteria are selected from the group consisting of staphylococcus spp., streptococcus spp., enterococci

spp., bacillus spp., corynebacterium spp., clostridia spp., peptostreptococcus spp., listeria spp. and legionella spp.

14. A method of treating or preventing aerobic and anaerobic bacterial infections in a mammal comprising administering to said mammal, a therapeutically effective amount of a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and are further substituted by a group represented by **R**, wherein R is H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6,R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

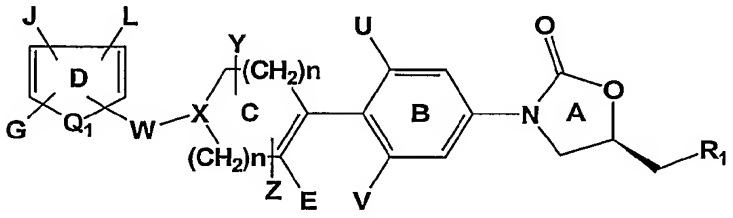
Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is $(CH_2)_{0-n'}$, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, S, $CH_2(CO)$, NH, O, NR_{11}, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2, SO, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_1 is - $NHC(=O)R_2$, $N(R_3, R_4)$, OR_3, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

15. A method of treating or preventing aerobic and anaerobic bacterial infections in mammal comprising administering to said mammal, a therapeutically effective amount of a compound having the structure of Formula II



Formula II

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3,R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

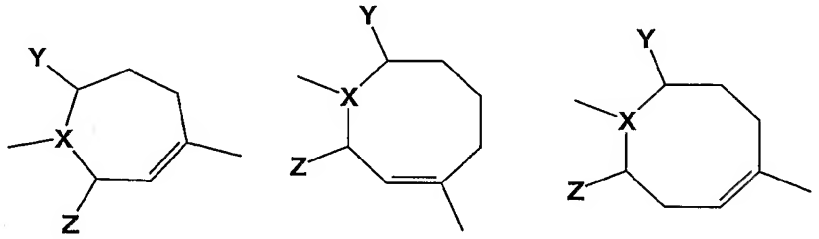
Q_1 is O, S or NR_{11}, wherein R_{11} is as defined above;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8,R_9,R_{10})$, $CON(R_6,R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, $-CH=N-OR_{10}$, $-C=CH-R_5$, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4, SR_4, wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently

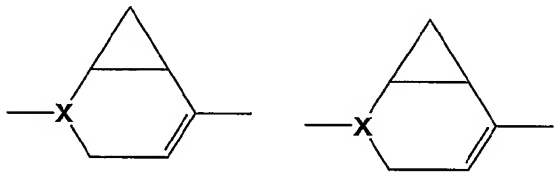
H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

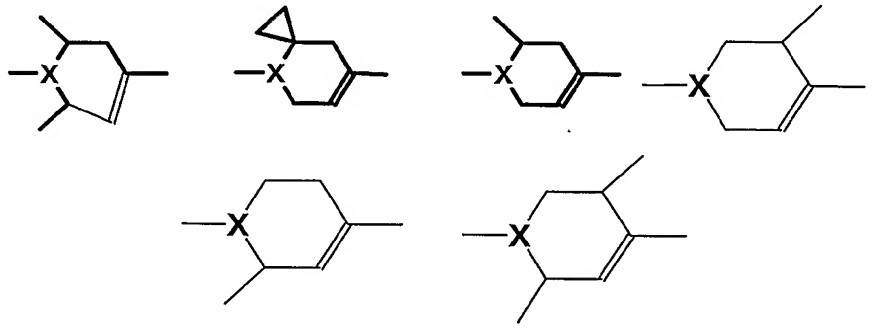
16. The method according to claim 15 wherein in Formula II, the ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, comprising



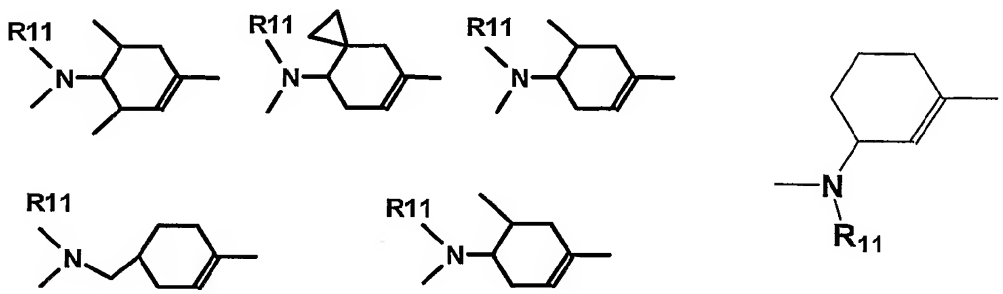
and the ring C may be bridged to form a bicyclic system as shown below:



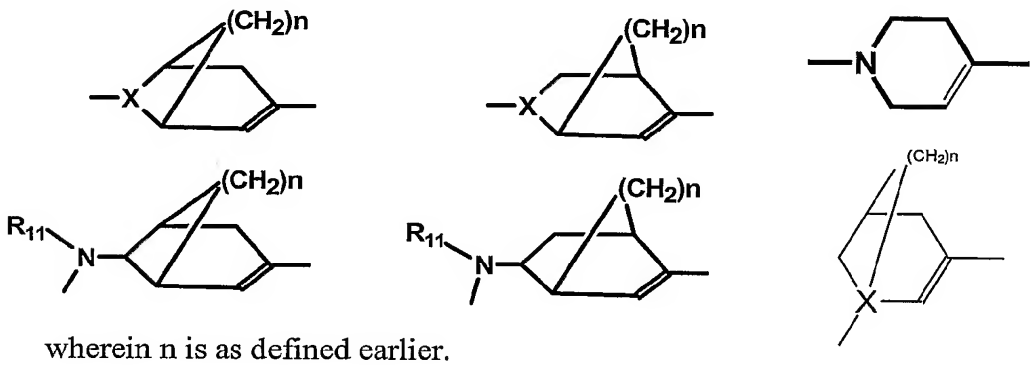
17. The method according to claim 15, wherein in Formula II, the ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below:



18. The method according to claim 15, wherein in Formula II, the ring C is 6-membered in size and X is -CH-(NHR), or -$CHCH_2NHR$-, the ring C is selected from the group consisting of the following rings wherein R_{11} is as defined earlier,

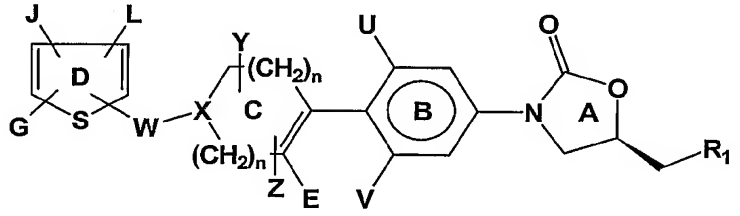


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

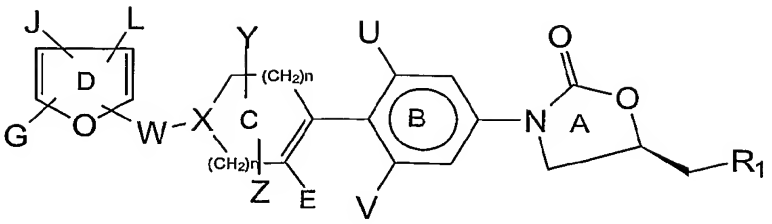
19. The method according to claim 15 having the structure of Formula III,



Formula III

wherein R_1, U, V, E, Y, Z, X, W, G, J, L and n are as defined earlier.

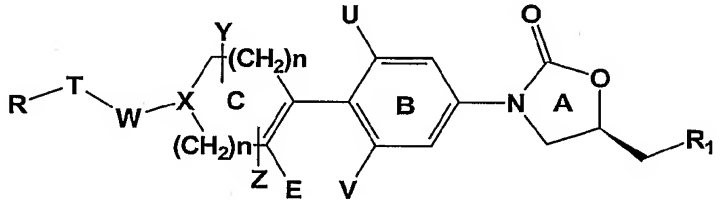
20. The method according to claim 15 having the structure of Formula IV



Formula IV

wherein R_1, U, V, X, Y, Z, W, G, J, L, E and n are as defined earlier.

21. A process for preparing compounds of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and further substituted by a group represented by **R**, wherein R is H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8,R_9,R_{10})$, $CON(R_6,R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5, SR_4,

$N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

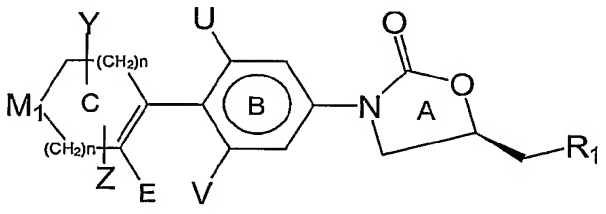
Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is $(CH_2)_{0-n'}$, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2$-$N(R_{11})CH_2$-, $CH_2(R_{11})N$-, $CH(R_{11})$, S, $CH_2(CO)$, NH, O, NR_{11}, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2, SO, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_1 is $-NHC(=O)R_2$, $N(R_3,R_4)$, OR_3, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

comprising reacting an amine compound of Formula V



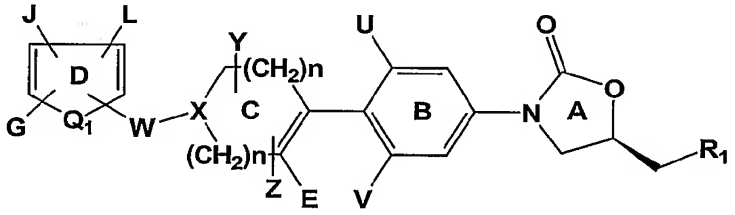
Formula V

with a heteroaromatic compound of Formula R-T-W-R_{12}, wherein M_1 is selected from the group consisting of NH, NHR_{13}, $-CH_2NR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R, T, W, R_1,U, V, Y, Z and E are as defined earlier and R_{12} is a suitable leaving group selected from the group consisting of fluoro, chloro, bromo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$, Tos, OC_6H_5, –COOH or –CHO.

22. The process according to claim 21 for preparing compounds of Formula I, wherein W=CH_2 and R-T-W-R_{12} is a heteroaromatic compound with an aldehyde group and the compound of Formula I is produced by reductive amination.

23. The process according to claim 21 for preparing compounds of Formula I, wherein W=CO and the amine compound of Formula V is acylated with activated esters in the presence of condensing agents selected from the group consisting of 1,3-dicylohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC).

24. A process for preparing compounds of Formula II



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is –NHC(=O)R_2, -N(R_3,R_4), –NR_2C(=S)R_3, –NR_2C(=S)SR_3 or –OR_3, wherein R_2, R_3, R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

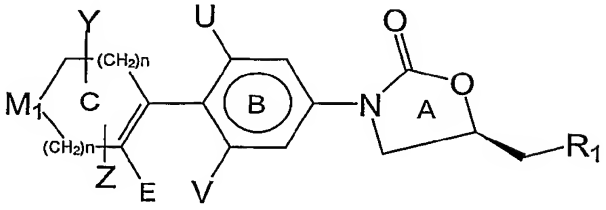
W is $(CH_2)_{0-n'}$, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, NR_{11}, $N(R_{11})C(=S)N(R_{11})$, wherein n′ is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

Q_1 is O, S or NR_{11}, wherein R_{11} is as defined above;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, –CN, COR_5, $COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8,R_9,R_{10})$, $CON(R_6,R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4, SR_4; wherein R_4 is the same as above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

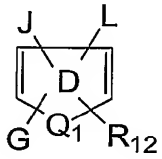
n is an integer in the range from 0 to 3;

comprising reacting a compound of Formula V



Formula V

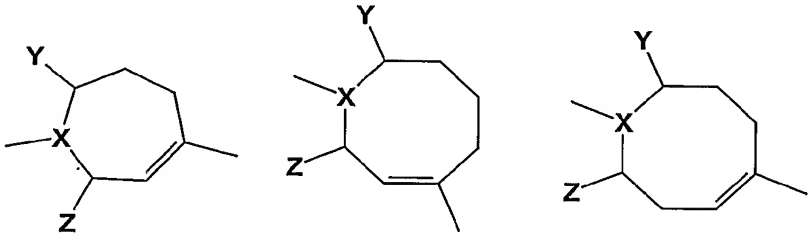
with a heteroaromatic compound of Formula VI



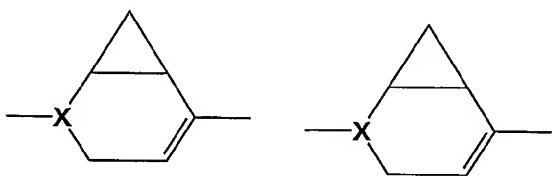
Formula VI

wherein M_1 is NH, NHR_{13}, $-CH_2NR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R, T, W, R_1,U, V, Y, Z, G, J, L, n, Q_1 and E are as defined earlier and R_{12} is a suitable leaving group selected from the group consisting of fluoro, chloro, bromo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$, Tos, OC_6H_5, –COOH or –CHO.

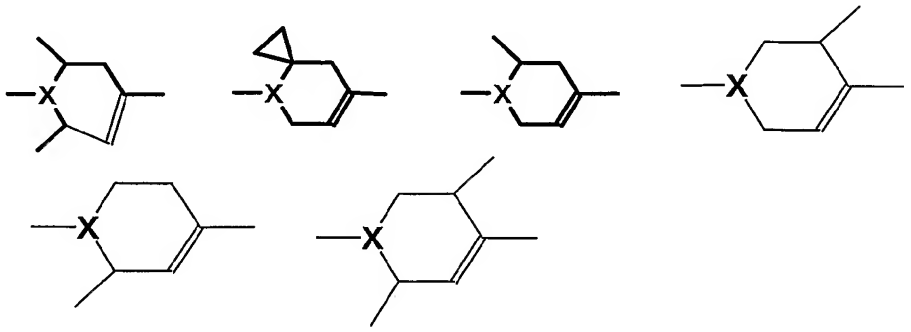
25. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, comprising:



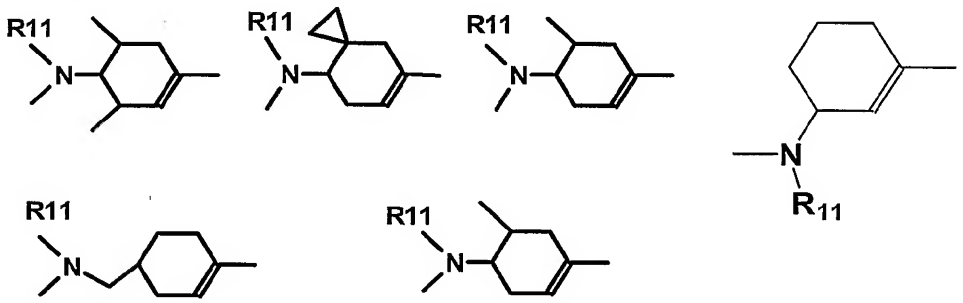
and the ring C may be bridged to form a bicyclic system as shown below:



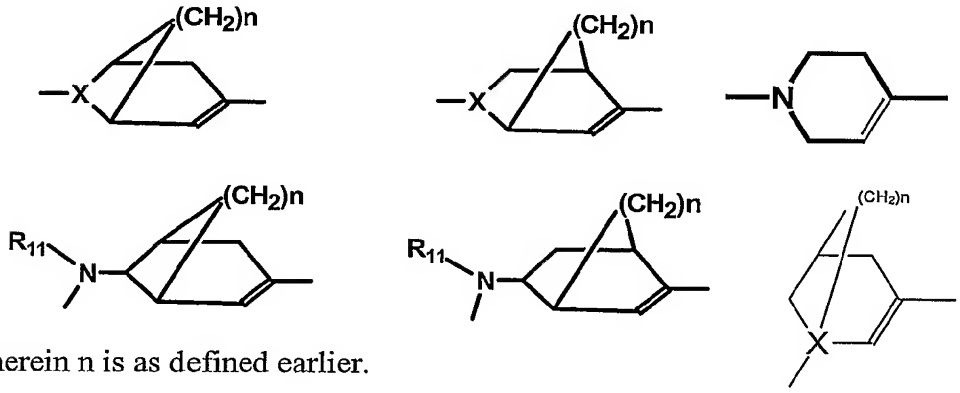
26. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below:



27. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is 6-membered in size and X is -CH-(NHR), or -$CHCH_2NHR$-, the ring C is selected from the group consisting of the following rings wherein R_{11} is as defined earlier;

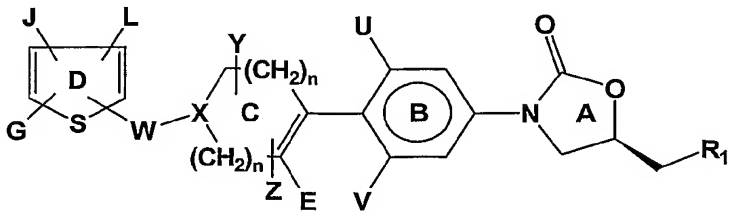


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

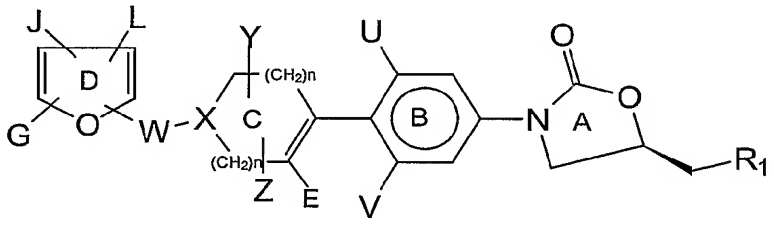
28. The process according to claim 24 having the structure of Formula III



Formula III

wherein R_1, U, V, Y, Z, E, X, W, G, J, L and n are as defined earlier.

29. The process according to claim 24 having the structure of Formula IV



Formula IV

wherein R_1, U, V, X, Y, Z, W, G, J, L, E and n are as defined earlier.

30. The process of claim 24, wherein the amine of Formula V reacts with a heteroaromatic compound of Formula VI in a solvent selected from the group consisting of dimethylformamide, dimethylacetamide, ethanol and ethylene glycol.

31. The process of claim 24, wherein the reaction of amine of Formula V with a heteroaromatic compound of Formula VI is carried out in the presence of a base selected from the group consisting of triethylamine, diisopropylamine, potassium carbonate and sodium bicarbonate.

32. The process of claim 24, wherein the reaction is carried out at a temperature ranging from about -70°C to about 180°C.

33. The process of claim 24, wherein the heteroaromatic compound of Formula VI is furaldehyde.

34. The process of claim 24, wherein the heteroaromatic compound of Formula VI is 2- furoic acid.

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/IB 03/01754

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 A61K31/422 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003 027083 A (MERCK & CO., INC., USA;KYORIN PHARMACEUTICAL CO., LTD.) 3 April 2003 (2003-04-03) claim 6; example 134 ---	1,9-14, 21-23
X	WO 99 64417 A (ZENECA LIMITED, UK) 16 December 1999 (1999-12-16) Claims and compounds of ex. 3, 11, 13, 15, 17, 26, 28, 31, 32, 34, 59, 131, 133, 137 and 167. ---	1,9-14, 21-23
X	WO 97 30995 A (ZENECA LTD., UK;GRAVESTOCK, MICHAEL BARRY) 28 August 1997 (1997-08-28) cited in the application claims, compounds of examples 12-13, 25-26, 37-38 and several compounds of table A p. 79 and table B p.81-82 --- -/--	1,2,6, 9-15,19, 21-24, 28,30-32

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2003	21/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gregoire, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati oplication No
PCT/IB 03/01754

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000 021960 A (ZENECA LIMITED, UK) 20 April 2000 (2000-04-20) cited in the application claim 6; example 47	1,9-14, 21-23
X	WO 99 10342 A (ZENECA LIMITED, UK) 4 March 1999 (1999-03-04) claims 1,2	1,9-14, 21-23
X	WO 97 09328 A (UPJOHN CO., USA;HUTCHINSON, DOUGLAS, K.; ENNIS, MICHAEL D.; HOFFMAN, R) 13 March 1997 (1997-03-13) claims 1,2	1,9-14, 21-23
X	WO 2003 072575 A (ASTRAZENECA AB, SWED.;ASTRAZENECA UK LIMITED) 4 September 2003 (2003-09-04) Intermediates 54 and 57 on pages 107 and 111	1,21-23
X	WO 2002 096916 A (ASTRAZENECA AB, SWED.;ASTRAZENECA UK LIMITED) 5 December 2002 (2002-12-05) Intermediates of steps 4 and 5 page 10	1,21-23

INTERNATIONAL SEARCH REPORT

Inte ıal application No.
PCT/IB 03/01754

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-20 are directed to a method of treatment of the human/animall body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-7(part), 9-34(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7(part), 9-34(part)

Claims 1-7 and 9-34, in as far as the expressions "prodrugs" and "metabolites" are explicitly or implicitly concerned, is so unclear (Article 6 PCT) that a meaningful international search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/IB 03/01754

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2003027083 A	03-04-2003	WO 03027083 A1	03-04-2003
		US 2003125367 A1	03-07-2003
WO 9964417 A	16-12-1999	AU 753988 B2	31-10-2002
		AU 4157199 A	30-12-1999
		BG 105001 A	28-09-2001
		BR 9910971 A	13-02-2001
		CA 2333332 A1	16-12-1999
		CN 1311787 T	05-09-2001
		EE 200000707 A	15-04-2002
		EP 1082323 A2	14-03-2001
		WO 9964417 A2	16-12-1999
		HU 0103082 A2	28-10-2002
		JP 2002517498 T	18-06-2002
		NO 20006152 A	02-02-2001
		NZ 508174 A	31-10-2003
		PL 345162 A1	03-12-2001
		SK 18362000 A3	11-06-2001
		TR 200003595 T2	23-07-2001
		US 2003144263 A1	31-07-2003
		US 6617339 B1	09-09-2003
		ZA 200006694 A	18-02-2002
WO 9730995 A	28-08-1997	AU 1805397 A	10-09-1997
		EP 0882042 A1	09-12-1998
		WO 9730995 A1	28-08-1997
		JP 11514662 T	14-12-1999
		US 2002133022 A1	19-09-2002
		US 6271383 B1	07-08-2001
		US 6365751 B1	02-04-2002
		US 5981528 A	09-11-1999
		ZA 9701469 A	25-08-1997
WO 2000021960 A	20-04-2000	AU 754123 B2	07-11-2002
		AU 6113199 A	01-05-2000
		BR 9914379 A	07-08-2001
		CA 2342623 A1	20-04-2000
		CN 1322203 T	14-11-2001
		EP 1121358 A1	08-08-2001
		WO 0021960 A1	20-04-2000
		HU 0103929 A2	29-07-2002
		JP 2002527439 T	27-08-2002
		NO 20011738 A	07-06-2001
		NZ 510211 A	30-05-2003
		US 2003207899 A1	06-11-2003
		ZA 200102659 A	01-07-2002
WO 9910342 A	04-03-1999	EP 1005468 A1	07-06-2000
		WO 9910342 A1	04-03-1999
		JP 2001514178 T	11-09-2001
		US 6605630 B1	12-08-2003
WO 9709328 A	13-03-1997	AT 207487 T	15-11-2001
		AU 716493 B2	24-02-2000
		AU 6718196 A	27-03-1997
		BR 9610474 A	02-03-1999
		CA 2228647 A1	13-03-1997
		CN 1197457 A ,B	28-10-1998

INTERNATIONAL SEARCH REPORT

Internati pplication No
PCT/IB 03/01754

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9709328 A		CZ 9800493 A3	12-08-1998
		DE 69616366 D1	29-11-2001
		DE 69616366 T2	04-07-2002
		DK 856002 T3	11-02-2002
		EP 0856002 A1	05-08-1998
		ES 2165516 T3	16-03-2002
		FI 980452 A	27-02-1998
		HK 1014946 A1	01-03-2002
		HU 9901979 A2	28-02-2000
		JP 11512386 T	26-10-1999
		NO 980855 A	30-04-1998
		NZ 315469 A	28-01-2000
		PL 325152 A1	06-07-1998
		PT 856002 T	29-04-2002
		RU 2175324 C2	27-10-2001
		SI 856002 T1	30-04-2002
		SK 19598 A3	04-11-1998
		TW 419468 B	21-01-2001
		WO 9709328 A1	13-03-1997
		US 6166056 A	26-12-2000
		US 6051716 A	18-04-2000
		US 6043266 A	28-03-2000
		US 6313307 B1	06-11-2001
		US 5968962 A	19-10-1999
		US 6358942 B1	19-03-2002
		ZA 9606935 A	16-02-1998
WO 2003072575 A	04-09-2003	WO 03072575 A1	04-09-2003
WO 2002096916 A	05-12-2002	WO 02096916 A1	05-12-2002